

Introduction to Immunology

Introduction

Immunology, more than any other subject in the Basic Sciences, is a web of interconnected topics. Every new component learned inherently references another part of the immune system, which means that there really isn't a starting point. And this means this will feel frustrating at the start, with obvious gaps and simple references that cry out for more detail. Don't chase the details that we've held back—we'll provide them at the appropriate time. The Immunology module is meant to be learned in the sequential order it's listed on the site and in the notes. Stay in order.

Because the immune system is nonlinear, and feedback and feedforward happen at so many levels, we start by demonstrating that interconnectivity, setting out the framework to build and grow upon. By the end, the material will feel comfortable. Let it come one bit at a time. And if you can, blast through Immunology in a few days, doing nothing else, so you can feel the connections.

For new learners, vocabulary can be challenging. Getting this fact straight now will help unburden your learning. **Leukocytes** means all white blood cells, and all cells of immunity—adaptive and innate. **Lymphocytes** means B cells, T cells, and NK cells. B cells, T cells, and NK cells all come from a common lymphoid progenitor. Just like all dogs are animals but not all animals are dogs, all lymphocytes are leukocytes but not all leukocytes are lymphocytes.

Organs of Immunity

The **primary** lymphoid organs (bone marrow and thymus) are where leukocytes **mature**. “Mature” means “are made.” All leukocytes mature in the primary lymphoid organs. The **bone marrow** is the primary lymph organ where **B** cells (and all other leukocytes) **mature**. As previously mentioned, T cells and B cells come from a common lymphoid progenitor. T cells originate from the same common lymphoid progenitor as B cells, but they are released from the bone marrow as very young and undeveloped prothymocytes. The prothymocyte is sent to the thymus to mature. Therefore, the **thymus** is the primary lymphoid organ where immature prothymocytes mature into **T** cells. Think of the thymus as boot camp for a soldier T cell. The soldier starts its life at home in the bone marrow where it matures until it is ready to leave for training in the thymus. As you will see, it is in the thymus that the T cell learns to do its job, just as a soldier learns skills in training.

The **secondary** lymphoid organs are the **lymph nodes**, **spleen**, and various sites where a cluster of lymphocytes (B cells and T cells) gathers and waits for the signal from the innate immune system that a response is needed. The nodes and spleen are the forward command posts for T and B cells, where they wait for a wayward antigen, or, more importantly, for a front-line troop to bring back intelligence. Soldiers from the front (APCs from the innate immune system, for example) bring information (antigens) back to these secondary lymphoid organs. The B cells and T cells assess the antigen and then activate themselves to proliferate or react to the antigen. If they see pathogens, antigen-presenting cells, or defective or dying self-cells, they carry out a robust immune response. The secondary lymphoid organs are therefore the site of industrial machinery, producing more advanced and specialized weapons of war in mass numbers against the specific pathogen.

| PRIMARY LYMPHOID TISSUE | SECONDARY LYMPHOID TISSUE |
|---|---|
| Role: T- and B-cell maturation | Role: T- and B-cell activation |
| Location: <ul style="list-style-type: none"> • Bone marrow for B-cell maturation • Thymus for T-cell maturation | Location: Lymph nodes, spleen, MALT, adenoids, tonsils |

Table 1.1: Primary vs. Secondary: Lymphoid Tissue—Lymphocytes

Immune System, Categorized

The immune system is divided into two branches: the innate and the adaptive.

The **innate immune system** functions primarily through **phagocytes**, **granulocytes**, and **complement**. It is **nonspecific**, **always on**, and has **no memory**. The innate immune system is able to activate the adaptive immune system, but can always function even without the adaptive immune system. The problem is that it isn't very robust, powerful, or targeted...and it can't learn—no matter how many times it encounters the same pathogen, it can't do anything better the next time. The cells of the innate immune system are the grunts, the foot soldiers, the front-line troops. Necessary, sometimes sufficient, but completely untrained, patrolling the perimeter, there to provide the first line of defense and reconnaissance. They phagocytose and kill pathogens, both of which are enhanced by the involvement of the adaptive immune system.

The **adaptive immune system** is **specific** and must be **activated by the innate immune system**, but has **memory**, making it easier to respond quickly the next time. The adaptive immune system makes the innate immune system work better and harder, and has some tricks of its own. The adaptive immune system comprises the mass-produced, specialized soldiers based on the information received from the front line. Equipped with an army of these specialized soldiers, each one good at fighting one specific antigen really well, but with many versions many times over, the adaptive immune response is robust and powerful.

The adaptive immune system is subsequently divided into **cellular** (mediated by **T cells**) adaptive immunity and **antibody** (mediated by **B cells**) adaptive immunity. T cells kill cell-to-cell with cytokines. B cells make antibodies. Even though that's the delineation, don't be fooled. The interactions between the different lymphocytes make it far more complicated than "one is T and the other is B." The complexity of these interactions is what makes up the rest of the Immunology module. It's easy once you get it, but it's hard to get while you're in it.

Innate Immunity

Innate immunity is fast, nonspecific, and always "on." It's our first line of defense. There are **anatomic barriers** (epithelium, mucosa), **physiologic barriers** (temperature, pH), and **cellular barriers**. The cellular barriers, the cellular defenses of innate immunity, include phagocytic cells, complement cascade, and NK cells. NK cells, in addition to killing viruses, kill tumor cells. **Phagocytosis** and subsequent intracellular destruction of pathogens in lysosomes are the predominant features of this type of immunity. "Phagocyte" is a vague term right now, but it will be fleshed out with details in the coming lessons. The point is that innate immunity is carried out by cells that eat other cells.

| IMMUNE BARRIER | EXAMPLE |
|----------------------|------------------------------|
| Anatomic barriers | Skin, mucosa, cilia |
| Physiologic barriers | Temperature, pH |
| Phagocytic cells | Macrophages, neutrophils |
| Natural Killer cells | Viral particles, tumor cells |

Table 1.2: Immune Barriers

Sometimes, spies from the front—innate immune cells called antigen-presenting cells (APCs)—bring pieces of destroyed pathogens back to the forward command post (the secondary lymphoid organs), where the lymphocytes are waiting. Adaptive immunity starts with the presentation of an antigen by an APC to the lymphocytes in a lymph node.

Activation of Adaptive Immunity

Adaptive immunity is carried out by lymphocytes—NK cells, B cells, and T cells. We’re going to focus on B cells and T cells exclusively, so from this point forward, “lymphocyte” implies B cells and

T cells. Many specifics are required to master their function, and they are studied in detail in subsequent lessons. For now, know that these cells are **highly specific** and need to be activated in an equally specific way by a specific antigen. This high specificity in activation protects against being activated to respond too quickly. But when they activate, they are really good at fighting whatever antigen they were shown that activated them.

Most phagocytic cells act as warriors, ingesting, digesting, and destroying pathogens at the site in tissue. A select few—APCs—act as runners, messengers that carry information from the front lines back to HQ. APCs digest and present pieces of the enemy to the B cells and T cells in secondary lymphoid centers. Once activated, T cells induce B cells to activate and proliferate. T cells also induce the release of cytokines, chemicals that influence phagocytes to work harder or chemicals that kill target cells (not all T cells and APCs are in the nodes; some are present in the periphery).

Effector Cells: T Cells and B Cells

An **effector cell** is **any cell** that carries out an immune response.

One effector cell type is the cytotoxic T cell. Cytotoxic T cells are the effector cells that release their own cytokines. These effector-cell cytokines can supercharge the innate immune system, activate the inflammatory response, or directly kill cells. Immunity mediated by cytotoxic T cells is called **cell-mediated immunity**. We left out a lot of mechanisms...but don’t worry, specifics will come later. T cells are covered in #9: *T-Cell Maturation* and #10: *T-Cell Activation*.

Another effector cell type is the antibody-producing B cell. B cells can act as APCs as well. In this case, B cells have surface immunoglobulins that bind antigen. If there’s a **costimulatory signal** (the B cell and the T cell agree that this antigen is a pathogen), then a separate lineage of T-helper cells induces **clonal expansion** of the B cell, forming **antibody-secreting plasma cells** to fight the current infection as well as storing **memory cells** with the antibody for later infection-fighting. This B-cell-antibody-mediated immunity is called **humoral immunity**; humoral is archaic. Say “antibody” instead. Humoral immunity got its name because the actions occurred in the humors of the body, the four chief fluids thought to determine a person’s physical and mental qualities by their relative proportions. Let’s start calling it **antibody immunity**. B cells are covered in #7: *B-Cell Maturation* and #8: *B-Cell Activation*.

Both cytotoxic T cells and antibody-secreting B cells constitute the adaptive immune system, and both are regulated by T-helper cells. Because adaptive immune responses are so specific and so robust when they do occur, it is important to have the checks and balances such as those which T-helper cells provide. Otherwise we might have an unnecessarily overreactive immune system.

Antibodies

B cells secrete antibodies. Antibodies are immunoglobulins, Y-shaped molecules with two Fab portions at the tips of the Y and an Fc portion at the bottom of the Y. The a, b, c alphabetical order is coincidence and stands for antigen-binding [Fab] and cytoplasmic [Fc] portions, based on their orientation in the plasma membrane when they act as membrane receptors in immature B cells. The tips (the Fab portions) bind antigen. The Fc portion at the bottom of the Y binds to a bunch of stuff. Fc can bind **complement**, which activates the complement cascade, poking holes in enemy cells, killing them. The Fc can bind **phagocyte receptors** (called opsonization), increasing the ease with which phagocytosis occurs (the phagocyte gets a tighter grip on the thing it's trying to eat). The Fc portion can just act as a barrier and prevent them from doing anything (physical contact is required for bad cells to act on good cells; if there's a coat of immunoglobulins, there's no physical contact). The Fc portion can also bind the **cell membrane** or the **cytoplasmic side** of a B cell. Fc: C = complement, phagocyte, cell, cell membrane, cytoplasmic. Immunoglobulins first start as **B-cell receptors** with their Fc portions acting as an anchor and transmembrane signal transducer. Once the B-cell is activated, it makes the same Y-shaped immunoglobulins in the form of an antibody and releases them through exocytosis.

Secreted immunoglobulins are antibodies. Fixed immunoglobulins are receptors.

There are many classes of antibodies. IgM is the antibody class responsible for the initial response to a foreign antigen. IgG is created after IgM responds to a foreign antigen, and is created for years after that foreign invader was first seen. Therefore, it provides long-term memory and long-term response. IgA is a mucosal antibody. IgE is the antibody class responsible for allergic reactions. IgD is the fail-safe that silences the lymphocyte.

| ANTIBODY | NOTES |
|----------|---|
| IgM | The first antibody made by all B cells. It is part of a premade repertoire of antibodies. |
| IgG | An antibody that is created in response to a foreign antigen. IgG is created for years after first recognition of an antigen, and circulates to help recognize foreign antigens more quickly the second time. |
| IgA | A mucosal antibody found in GI and respiratory tracts. |
| IgE | Mast-cell degranulation, parasite elimination, allergies |
| IgD | Marker of inactivation. Fail-safe for tolerance |

Table 1.3: Antibodies

Antibodies and their interaction with B cells and antigens are covered in detail in #6: *Antigens and Antibodies*.

Memory

The innate immune system has no memory. The adaptive immune system does. Clonal expansion of B cells leads to some of the clones being stored as memory cells. These can persist for years to decades. Re-exposure to the same antigen allows for a **rapid response** with **hyperspecific antibodies**—a response that took time the first time to go from nonspecific (in the sense that it was not created in response to a previously seen antigen) IgM to specific (made in response to a previously seen antigen) IgG. A rise in a specific titer of IgM is a marker for an acute infection with a new antigen. A rise in a specific titer of IgG is a marker for an acute infection (re-exposure to an old bad guy) **OR** immunity to an old antigen (old IgG hanging around waiting to attack that bad guy if he shows up again).

Autoimmunity

B cells and T cells are screened both for **function** (the body ensures they can do what they're supposed to, fight pathogens) and **tolerance** (the body ensures they won't turn on the self; they will tolerate antigens that belong in the organism, and fight only foreign pathogens). Basically, these soldiers need to be effective and strong, but not traitors.

Autoimmunity describes a loss of tolerance: the same immune responses that should occur against pathogens occur against self. This is covered in #14: *Autoimmunity*. Another form of abnormal immune response is hypersensitivity, covered in #11: *Hypersensitivity Reactions*.

Immunodeficiency is a loss of normal protective function of the immune system. The body, reliant on the robust immunity of the lymphocytes and innate immune system, cannot fight off pathogens as it should. This is covered in #15: *Immunodeficiency*.

Other Topics in Immunology

#12: *Transplant and Rejection* uses transplantation to review the entire system, and we explore different types of rejection. #13: *Vaccines* is used both to expose the student to the clinical vaccination series and to explore the value and purpose of memory in the adaptive immune system. #16: *Immunosuppression* discusses key regulatory steps in autoimmune disease and provides an overview of immunosuppressant agents.